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Original Article

Propofol in combination with remifentanil for cesarean section: Placental transfer and effect on mothers and newborns at different induction to delivery intervals

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ABSTRACT

Objective: This study aims to describe the administration of propofol in combination with remifentanil for the induction of general anesthesia during cesarean section (CS). Our aim was to evaluate its impact on the drug concentrations of the maternal and neonatal blood at different induction of anesthesia to delivery (I–D) intervals as well as its effect on newborns.

Materials and methods: In this double-blind randomized controlled study, patients undergoing elective CS were administered anesthesia at short (n = 20) or long (n = 20) I–D intervals. Anesthesia was induced with 1 mg/kg propofol and 1 μg/kg remifentanil and maintained by continuous infusion of 3 mg/kg/h propofol and 7 μg/kg/h remifentanil.

Results: The mean plasma propofol concentrations at delivery in the maternal arterial (MA) blood and the fetal umbilical arterial (UA) and venous (UV) blood in the short I–D interval group were 1.91, 1.17, and 0.51 μg/mL, respectively, while those in the long I–D interval group were 1.57, 1.07, and 0.61 μg/mL, respectively. The mean plasma remifentanil concentrations at delivery in the MA, UA, and UV in the short I–D interval group were 2.25, 1.43, and 0.65 ng/mL, respectively, and those in the long I–D interval group were 1.96, 1.25, and 0.75 ng/mL, respectively. There were no statistically significant differences in the neonatal Apgar scores and neurological adaptive capacity scores between the two groups.

Conclusions: It is safe to administer propofol in combination with remifentanil by continuous infusion after the bolus dose for the induction of anesthesia during cesarean section. Prolonging the I–D interval within a certain limit will not have any significant influence on the fetus.

Introduction

Patients with contraindications for regional anesthesia for cesarean section (CS) are anesthetized by general anesthesia, the greatest scruple of which is the effect of anesthetics on the newborns [1]. New and suitable anesthetic agents such as propofol [2–6] and remifentanil [7–11], which have favorable pharmacokinetic profiles and rapid onset and offset durations, have been used previously by various authors, at different dosages and with different methods of administration, for the induction and maintenance of anesthesia, especially in cases of severe maternal cardiovascular and cerebrovascular diseases [12,13], pre-eclampsia [14], hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome [15], in which the blunting of hypertension and tachycardia is believed to be crucial for maternal well-being. In the majority of these reports, no apparent major adverse effects of the anesthetics on the neonatal outcome at birth were described.

Propofol and remifentanil cross the placenta and are cleared from the neonatal circulation rapidly [2,6,7,10,16]. However, in the case reports mentioned above, as well as in several other studies, the plasma levels of the drugs and their potential adverse effects on the newborn at the time of delivery appear to be dependent on the dosage regimens used for induction and maintenance as well as on

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the time lapse between induction of anesthesia and delivery of the newborn. After single administration, propofol and remifentanil have been reported to exhibit transient plasma concentration peaks in mothers, followed by a rapid decline [2,6,7,17,18]. For example, a 2 mg/kg dosage of propofol was reported to appear in the maternal plasma at a peak concentration of 5.01 μg/mL a minute after administration; however, its plasma concentration at delivery, 8.4 min after bolus, was only 1.47 μg/mL [2], which was significantly lower than the minimum plasma concentration (1.64 μg/mL) at which propofol induces unconsciousness in adults [19]. Maintenance of anesthesia by the continuous infusion of remifentanil immediately after the single bolus dose could contribute to the maternal hemodynamic stability and reduce the occurrence of intraoperative awareness [9,20,21]. The combination of propofol and remifentanil has been reported to be more suitable for mothers at high risk of severe hemodynamic fluctuations [22]. Therefore, it is necessary to investigate the optimal method of administration and dosing regimen of these anesthetics during delivery.

In this study, we administered propofol in combination with remifentanil by continuous infusion after single bolus for the induction of general anesthesia for CS and analyzed the maternal and neonatal plasma concentrations of the anesthetics at the time of delivery in order to assess the rate of placental transfer of these two drugs and their effect on the mothers and newborns at different anesthesia induction to delivery (I–D) intervals.

Materials and methods

Study subjects and grouping

This study included 40 parturients with single births, between the ages of 21 and 40 years, pregnant for 37–41 weeks, and requiring elective CS under general anesthesia because of absolute or relative contraindications to regional anesthesia (ASA grades I and II). The exclusion criteria for this study were as follows: the presence of cardiorespiratory diseases, morbid obesity, diabetes, multiple gestation, premature rupture of membranes, and known fetal anomalies. This study was approved by the Ethics Committee of Anhui Provincial Hospital. Written informed consent was obtained from all participants.

We randomly allocated patients to one of two groups by drawing sequentially numbered sealed envelopes that each contained a computer-generated randomization code. Replacement randomization was performed when codes were generated to ensure equal numbers in each group. For the patients of group I, after disinfection and placement of the surgical towels, anesthesia was induced until the BIS of the patient dropped below 60 and consciousness was lost; tracheal intubation and CS were performed simultaneously. For the patients of group II, anesthesia was first induced, followed by disinfection and surgical towel placement.

Anesthetic procedures

All of the patients were orally administered 150 mg ranitidine the night before surgery as well as 2 h before surgery. Upon arrival in the operating room, standard monitoring including electrocardiography and non-invasive arterial pressure and pulse oximetry was applied, and the parturient was positioned supine with a 10–15° left lateral tilt. A radial arterial catheter was placed to measure the blood pressure and collect blood samples. The BIS was continuously monitored using a BIS monitor. An intravenous catheter was inserted into the forearm vein, and lactated Ringer's solution was infused. The patient was provided 6 L/min oxygen for spontaneous breathing until the start of anesthesia induction. Propofol (1 mg/kg; batch no.: JS275, AstraZeneca, Caponago, Italy) and remifentanil (1 μg/kg; batch no.: 6120905, Yichang Humanwell Pharmaceutical Co, Ltd, Hubei) were intravenously injected one after the other within 20–30 s. When the BIS of the patient reached ≤60 and consciousness was lost, 0.8 mg/kg rocuronium was intravenously injected. Following this, endotracheal intubation and mechanical ventilation (tidal volume, 8–10 mL/kg; frequency, 12–15 beats/min) were performed, and the $PetCO_2$ level was maintained at 30–40 mmHg. Immediately after bolus administration, 3 mg/kg/h propofol and 7 μg/kg/h remifentanil were continuously infused to maintain anesthesia, and a low concentration of sevoflurane was provided intraoperatively, if required, according to the depth of anesthesia.

Neonatal assessment

The induction-to-skin incision (I–S), I–D, and uterine incision-to-delivery (U–D) intervals were recorded using a stopwatch. After delivery, the neonatal Apgar score was assessed by a pediatrician blinded to the grouping of the patients, at the following three time points – immediately after delivery, 5 min after delivery, and 10 min after delivery. The concentrations of the gases in the umbilical arterial/venous blood, neonatal weight, necessity and duration of mask ventilation, and necessity for intubation of the newborn were recorded. The neurological adaptive capacity scores (NACS) of the newborns were assessed 15 min, 2 h, and 24 h after delivery.

Sampling and analytical method

Immediately after delivery, 3 mL each of maternal arterial (MA) and fetal umbilical arterial (UA) and venous (UV) blood were extracted. The samples were centrifuged in sodium citrate-coated anticoagulant tubes at 2000 rpm for 10 min, and the plasma was isolated and stored at −70 °C until analysis. The concentration of propofol in the plasma was determined by high performance liquid chromatography with fluorescence detection. The concentration of remifentanil was measured by ultra-performance liquid chromatography tandem mass spectrometry.

Statistical analysis

The statistical analyses were performed using SPSS version 16.0 for Windows. The measurement data were expressed as the mean ± standard deviation ($\bar{x}\pm s$). The concentrations of propofol and remifentanil and the results of the umbilical cord blood gas analysis were compared between the two groups using the Student's t-test. The comparison of the neonatal Apgar scores, NACS, and the resuscitative measures applied were compared between the groups using the chi-square test. The correlation of the I–D intervals with the plasma concentrations of propofol and remifentanil, Apgar scores, and NACS were evaluated in the two groups using the Spearman rank correlation test. Values of $P < 0.05$ were considered as indicating statistical significance.

Results

General information

The contraindications of regional anesthesia were similar between the patients of groups I and II and included placenta previa, refusal of regional anesthesia or contraindication for the same because of coagulation disorders, and presence of spinal deformities. The differences between the two groups in terms of the gestational week, patient age, height, body weight, U-D interval, and infant weight showed no statistical significance, but the I–S

and I–D intervals in group II were significantly longer than those in group I ($P < 0.05$; Table 1).

Placental transfer of propofol and remifentanil

There were no statistically significant differences between the two groups in terms of either the mean plasma propofol concentrations in the UV and UA blood or the mean UV/MA and UA/UV ratios of propofol concentration at delivery. However, the mean plasma propofol concentration in the MA blood in group II was lower than that in group I at delivery ($P < 0.05$). There were no statistically significant differences in either the mean plasma remifentanil concentrations in the MA, UV, and UA blood or in the mean UV/MA and UA/UV ratios of remifentanil concentration between the two groups at delivery (Table 2). The plasma remifentanil concentrations in the UA blood could not be evaluated in two patients in group I and three patients in group II because of the insufficient volume of the sampled blood.

Neonatal assessments

The mean I–D interval of group I ranged from 4.9 to 10.1 min and that of group II ranged from 13.2 to 22.6 min. There was no correlation between the I–D interval and the Apgar scores or NACS in either of the groups. However, the mean plasma concentrations of propofol and remifentanil in the MA blood were both negatively correlated with the I–D interval ($P < 0.05$; Figs. 1 and 2). The mean plasma propofol concentration in the UA blood was negatively correlated with the 15-min NACS ($P < 0.05$; Fig. 3) in both groups.

There were no statistically significant differences in the fetal umbilical arterial and venous blood gas concentrations between the two groups (Table 3). The differences between the two groups in terms of the Apgar scores, NACS, and the number of the newborns requiring resuscitation were also not statistically significant (Table 4). Respiratory depression after delivery was observed in five newborns in group I and four in group II; although they showed no improvement despite stimulation by touch and slapping of the sole, they recovered spontaneous breathing after administration of oxygen supply with a bag mask. Tracheal intubation was not performed in any of the newborns in the two groups.

Discussion

Because propofol and remifentanil are short-acting intravenous anesthetics, their maintenance dosages should be administrated at timely intervals after the induction of anesthesia. In a previous study, after the induction of anesthesia with 2.5 mg/kg propofol, followed by the administration of 5 mg/kg/h propofol for the maintenance of anesthesia, with an I–D interval of 20.2 min to achieve the required depth of anesthesia, the concentration of propofol in the MV blood at delivery was reported to be 1.66 μg/mL; however, some of the newborns experienced respiratory depression [6]. Bouattour et al. [9] reported that the administration of 2 mg/kg propofol in combination with 0.5 μg/kg remifentanil, followed by a combination of 6 mg/kg/h propofol and 12 μg/kg/h remifentanil, would not generate significant neonatal depression. In the study by Van de Velde et al. [21], administration of 5 μg/mL propofol in combination with 0.5 μg/kg remifentanil and 2.5 μg/mL propofol in combination with 12 μg/kg/h remifentanil was reported to be able maintain the stability of maternal hemodynamics without apparent neonatal depression. Based on the findings reported in literature and the results of our preliminary experiments, we administered 1 mg/kg propofol in combination with 1 μg/kg remifentanil for the induction of anesthesia and 3 mg/kg/h propofol in combination with 7 μg/kg/h remifentanil for the maintenance of anesthesia, in the present study. At delivery, the mean concentrations of remifentanil in the MA blood in groups I and II were 2.25 and 1.96 ng/mL, respectively; these concentrations were higher than that (1.67 ng/mL) required for the effective attenuation of the hypertensive response to tracheal intubation in patients during CS [20]. The mean concentrations of propofol in the MA blood at delivery in groups I and II were 1.91 and 1.57 μg/mL, respectively, which were higher than the minimum plasma concentration of propofol at which adults lose consciousness [19]; therefore, there were no incidents of intraoperative awareness reported by the patients in either of the groups during postoperative follow-up. The

Table 1
General information and operation time of the two groups ($n = 20$, $\bar{x}\pm s$).

	Group I	Group II	*P*
Age, years	30 ± 6.0	31 ± 6.5	0.75
Body weight, kg	70 ± 8.2	68 ± 7.3	0.79
Height, cm	162 ± 3.8	161 ± 4.1	0.52
Gestation, weeks	39.1 ± 1.1	38.8 ± 0.9	0.75
I–S, min	2.7 ± 0.7	13.3 ± 1.6	<0.0001
I–D, min	6.9 ± 1.2	18.0 ± 1.9	<0.0001
U–D, s	120.6 ± 17.8	108.9 ± 13.9	0.21
Infant weight, g	3276 ± 269.9	3224 ± 257.1	0.79

Table 2
Plasma concentrations of propofol and remifentanil in the two groups ($n = 20$, $\bar{x}\pm s$).

	Propofol, μg/ml			Remifentanil, ng/ml		
	Group I	Group II	*P*	Group I	Group II	*P*
MA	1.91 ± 0.46	1.57 ± 0.30	0.03	2.25 ± 0.46	1.96 ± 0.43	0.09
UV	1.17 ± 0.29	1.07 ± 0.19	0.32	1.43 ± 0.36	1.25 ± 0.24	0.12
UA	0.51 ± 0.17	0.61 ± 0.10	0.08	0.65 ± 0.11	0.75 ± 0.18	0.12
UV/MA ratio	0.63 ± 0.09	0.69 ± 0.07	0.07	0.63 ± 0.07	0.65 ± 0.09	0.51
UA/UV ratio	0.47 ± 0.07	0.52 ± 0.07	0.06	0.49 ± 0.07	0.56 ± 0.11	0.10

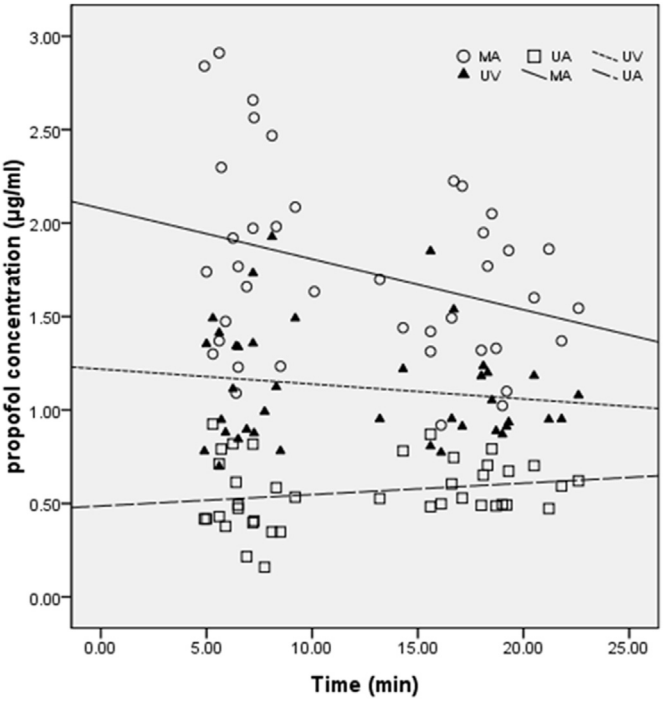

Fig. 1. Correlations of maternal and neonatal blood concentrations of propofol with I–D time. MA: r = −0.33, $P = 0.04$; UV: r = −0.16, $P = 0.31$; UA: r = 0.18, $P = 0.25$.

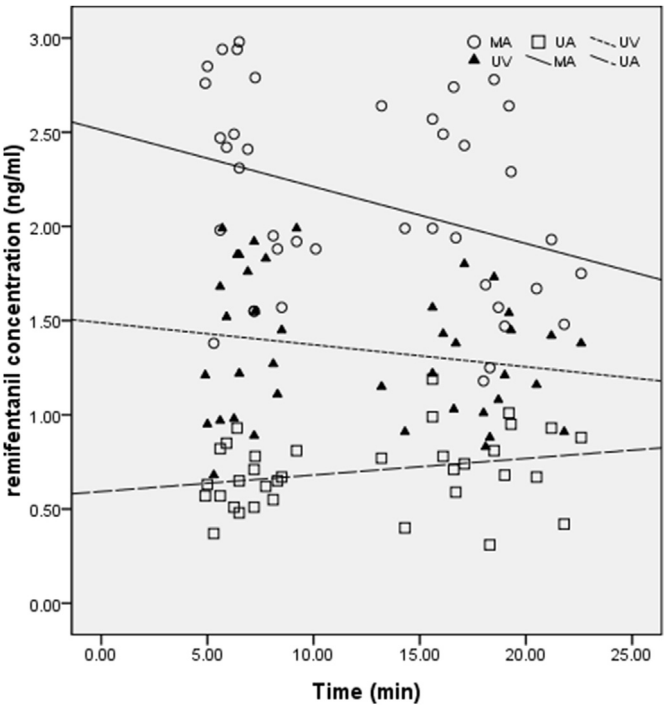

Fig. 2. Correlations of maternal and neonatal blood concentrations of remifentanil with I–D time. MA: r = −0.35, $P = 0.03$; UV: r = −0.18, $P = 0.26$; UA: r = 0.26, $P = 0.12$.

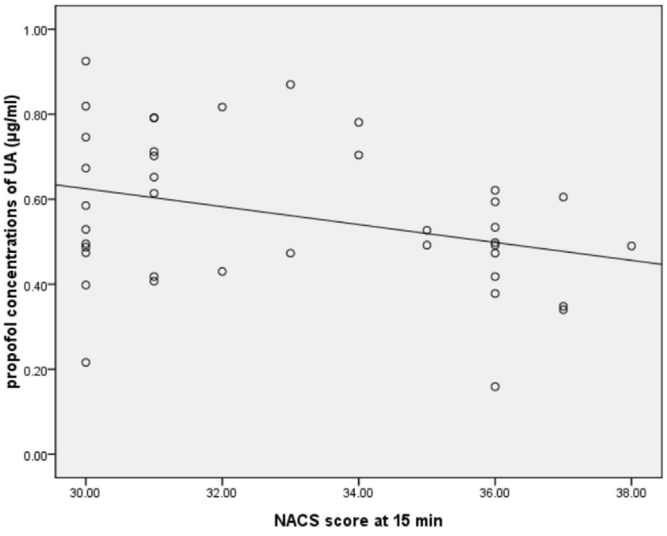

Fig. 3. Correlations of plasma propofol concentration in UA with neonatal NACS 15 min after delivery (r = −0.33, $P = 0.04$).

anesthetic dosages administered in the present study were lower than those reported in a few previous studies [4–6,8,9], and a possible reason for this discrepancy might be that the anesthetic dosages used in this study considered the total maternal body weight instead of the lean body mass [5,6]. In addition, the dosages of anesthetics administered to Chinese individuals might be lower than those administered to people of European and American origins [23]. Although the dosages of propofol used in the present study were lower than those reported for the induction and maintenance of anesthesia in the previous studies that used propofol alone [4,6], the maternal plasma concentrations of propofol observed in our study were close to those reported in those studies,

Table 3
Analysis and comparison of fetal umbilical arterial and venous blood gas between the two groups ($n = 20$, $\bar{x}\pm s$).

	Group I	Group II	*P*
Umbilical artery blood			
pH	7.26 ± 0.03	7.28 ± 0.04	0.35
PaO_2, mmHg	21.1 ± 3.7	22.5 ± 5.0	0.41
$PaCO_2$, mmHg	56.5 ± 6.3	57.1 ± 4.9.	0.77
BE	−2.8 ± 1.3	−2.2 ± 1.1	0.23
Umbilical vein blood			
pH	7.29 ± 0.05	7.32 ± 0.04	0.15
PaO_2, mmHg	37.5 ± 8.4	38.2 ± 8.1	0.84
$PaCO_2$, mmHg	49.1 ± 6.6	48.4 ± 5.1	0.73
BE	−2.2 ± 1.3	−2.6 ± 1.8	0.50

Table 4
Comparison of neonatal scores and resuscitative measures between the two groups ($n = 20$).

	Group I	Group II	*P*
Apgar scores at 1 min			0.91
10	4 (20%)	5 (25%)	
8–9	9 (45%)	9 (45%)	
5–7	7 (35%)	6 (30%)	
Apgar scores at 5 min			0.54
10	14 (70%)	12 (60%)	
8–9	6 (30%)	7 (35%)	
7	0 (0%)	1 (5%)	
Apgar scores at 10 min			1.00
10	20 (100%)	20 (100%)	
NACS			
≥35 at 15 min	7 (35%)	8 (40%)	0.74
≥35 at 2 h	16 (80%)	15 (75%)	0.71
≥35 at 24 h	20 (100%)	20 (100%)	1.00
Resuscitative measures			
Tactile stimulation	13 (55%)	11 (40%)	0.52
Bag–mask ventilation	5 (25%)	4 (20%)	0.71
Tracheal intubation	0 (0%)	0 (0%)	1.00

probably because of the mutual pharmacokinetic inhibitory relationship between propofol and remifentanil. A previous study [24] had shown that the pharmacodynamics relationship between propofol and remifentanil was synergetic, while their pharmacokinetic relationship indicated mutual inhibition; therefore, when these two drugs are concurrently used, both their plasma concentrations would be high.

The plasma concentration of propofol in the UA blood is close to that acting on the fetal brain. It has been reported that, 5 min after the induction of anesthesia with a single bolus injection of 2.5 mg/kg propofol, the plasma concentration of propofol in the UA blood could be as high as 1.79 μg/mL [17], which is higher than the average concentration at consciousness (0.973 μg/mL) in children sedated with propofol (who ranged in age from 5 months to 8 years) [25]. The reduction of the induction dose of propofol (2 mg/kg) [18] and the extension of the I–D interval (25.9 min) [6] have been reported to decrease the concentration of the anesthetic in the UA blood (0.6 μg/mL and 0.42 μg/mL, respectively). In our study, upon the administration of propofol at a concentration of 3 mg/kg/h after a bolus of 1 mg/kg, the mean plasma concentrations of propofol in the UA blood at delivery, at mean I–D intervals of 6.9 min and 18 min, were 0.51 μg/mL and 0.61 μg/mL, respectively; these values are significantly lower than the concentration of propofol required for sedation in children [25]. The plasma propofol concentration in the UA blood was negatively correlated with the 15-min NACS. The 10-min Apgar scores of all of the newborns were >10, and the 24-h NACS were >35. Although there were a few cases of temporary respiratory depression among the newborns in groups I (n = 5) and II (n = 4), the affected newborns quickly

recovered spontaneous breathing after oxygen administration with a bag mask; none of the newborns in either of the groups required tracheal intubation.

Because of the discrepancies in either the method and dosing of propofol administration or the I–D intervals, the differences reported in the UV/MA ratios of propofol concentration have been relatively great (0.22–0.85) [2,4,6,16–18]. In the present study, the UV/MA ratios of propofol concentration in groups I and II were 0.63 and 0.69, respectively, indicating that propofol could diffuse through the placenta rapidly. The UA/UV ratios of propofol concentration in groups I and II were 0.47 and 0.52, respectively; these values are similar to those reported in previous studies involving single induction followed by the continuous infusion of propofol [4,6], suggesting the possibility of continuous uptake of propofol by fetal tissues. However, bolus induction studies with longer I–D intervals have reported UA/UV ratios of 1.09 [6] and 1.07 [16], which indicate more extensive fetal distribution as well as redistribution from the fetus to the mother; this might be because propofol is eliminated faster by parturient subjects than newborns [26] and the metabolism of propofol in newborns is significantly slower than that in adults [6,18].

Pharmacokinetic data on the use of remifentanil in CS are scarce. Upon single-bolus dose induction with 1 μg/kg remifentanil for 12.9 min [7] or continuous infusion with 6 μg/kg/h remifentanil for 15 min [10], the UV/MA ratios for remifentanil concentration at the time of delivery were reported to be 0.73 and 0.88, respectively. Additionally, the results of a study on obstetric analgesia using remifentanil for more than 2 h revealed that, even upon reaching steady-state plasma levels, the UV/MA ratio for remifentanil concentration was 0.7 [27]. In our study, the UV/MA ratios for remifentanil concentration in groups I and II were 0.63 and 0.65, respectively, indicating that remifentanil could readily pass through the placenta. The UA/UV ratios for remifentanil concentration in groups I and II were 0.49 and 0.56, respectively; these values were greater than those that reported by Kan et al. [10] and Shen et al. [27] (0.29 and 0.26, respectively) and lower than those reported by Ngan et al. (0.6) [7], indicating that remifentanil could be metabolized and redistributed in the fetus and differences in the dosing regimens might affect the UA/UV ratio. Furthermore, the mean remifentanil concentrations in the UA blood in groups I and II in the present study were 0.65 and 0.75 ng/mL, respectively; they were both lower than the concentration at which spontaneous ventilation has been reported to occur (1.05 ng/mL; range, 0.97–1.14 ng/mL) [28].

One of the biggest scruples in the administration of general anesthesia is the effect of anesthetics on neonatal respiratory systems. It is traditionally believed that the shorter the I–D interval, the higher the neonatal Apgar score [16]. Because propofol and remifentanil can rapidly pass through the placental barrier and enter the fetal circulation, the mother and fetus might achieve peak plasma concentrations of the anesthetics within 5 min of induction of anesthesia [2,4,17]. At extended I–D intervals, the process of continuous uptake and redistribution of the anesthetics in the maternal circulation could gradually cause a decline in the blood anesthetic concentrations in the fetus. The results of the present study showed that the plasma concentrations of propofol and remifentanil in the UV and UA blood were not correlated with the I–D interval; however, their plasma concentrations in the MA blood were negatively correlated with the I–D interval, indicating that continuous anesthetic infusion after bolus along with the extension of the I–D interval would prevent drug accumulation in the mother and fetus. A possible reason for this result is that, following single-dose administration, once the peak concentrations of anesthetics are achieved, the drug plasma concentrations could gradually decrease; additionally, the rate of continuous infusion of anesthetics could be lower than its elimination rate. Therefore, the administration of short-acting anesthetics and application of appropriate I–D intervals could ensure the safety of the mother and fetus during CS. However, further studies are required to evaluate whether the extension of the I–D interval would cause a gradual increase in the concentrations of propofol and remifentanil in the UA blood and also to estimate the delivery time point at which the maternal and neonatal blood concentrations would be the lowest and, consequently, the negative impact on the mother and newborn would be the smallest.

Traditionally, general anesthesia is induced using thiopental and succinylcholine with maintenance of anesthesia before delivery of the fetus using nitrous oxide and low concentrations of inhalation agents to avoid the potential for neonatal depression. Although routinely opioids are not drugs of choice in induction of general anesthesia during cesarean section, little amounts of fentanyl is administered in special cases [14]. Disadvantages of this technique include maternal awareness, inadequate analgesia and hypertensive responses following laryngoscopy, tracheal intubation and incision [21]. The rapid redistribution of single induction dose underlines the importance of introducing an adequate volatile anesthetic as soon after induction as is practical. There may be insufficient time to allow adequate uptake and distribution of volatile anesthetic to prevent awareness before redistribution causes brain levels of the induction drug to decrease. The use of higher concentrations of a volatile halogenated agent has subsequently become a more common practice, leading to a lower incidence of maternal awareness, but there are concerns about neonatal depression and uterine atony in a dose-dependent manner, particularly when the I–D interval exceeds 8 min [29,30]. The incidence and severity of above-mentioned problems can be reduced using suitable agents such as remifentanil and propofol, which have a favorable pharmacodynamic and pharmacokinetic profile characterized by the rapid onset and offset for obstetric anesthesia. However, our study has some limitations. It is difficult to make some comparisons of general anesthesia by using propofol in combination with remifentanil or traditional general anesthesia by using gas (sevoflurane or desflurane) with fentanyl between two groups (short and long I–D interval), which need further study.

Conflict of interest

All authors have no conflict of interest regarding this paper.

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